Haem-Match

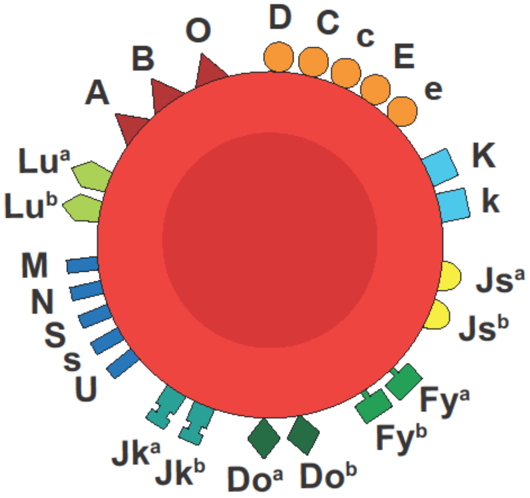
Dr Sara Trompeter
Consultant Haematologist UCLH and NHSBT
Cambridge Symposium
30 September 2024

So far, we have heard that:

Many patients with haemoglobin disorders need transfusions with very little other treatment options

Patients with sickle cell have a high incidence of new antibody formation

We are transfusing a lot of blood

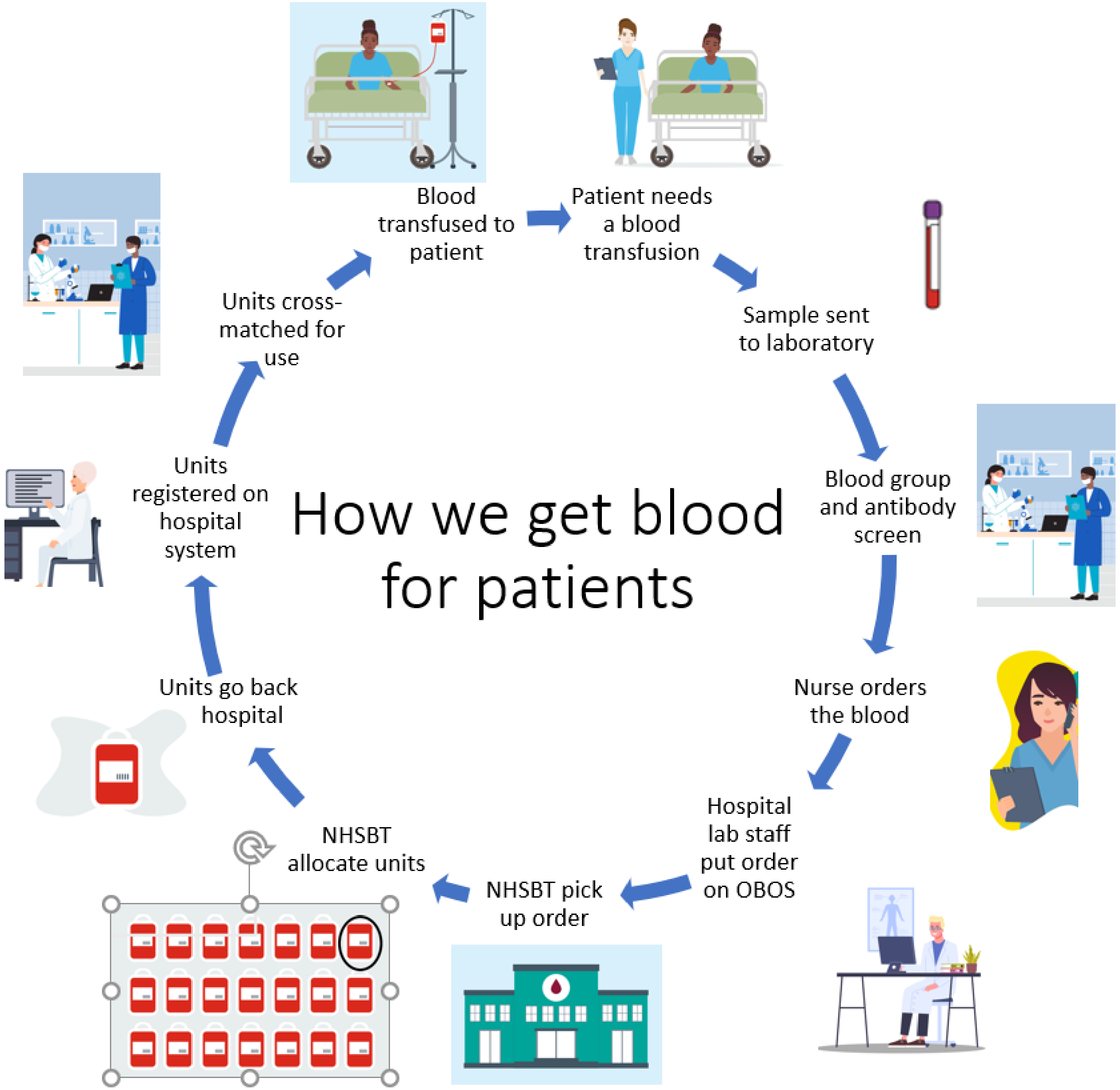


There are a lot of red cell antigens

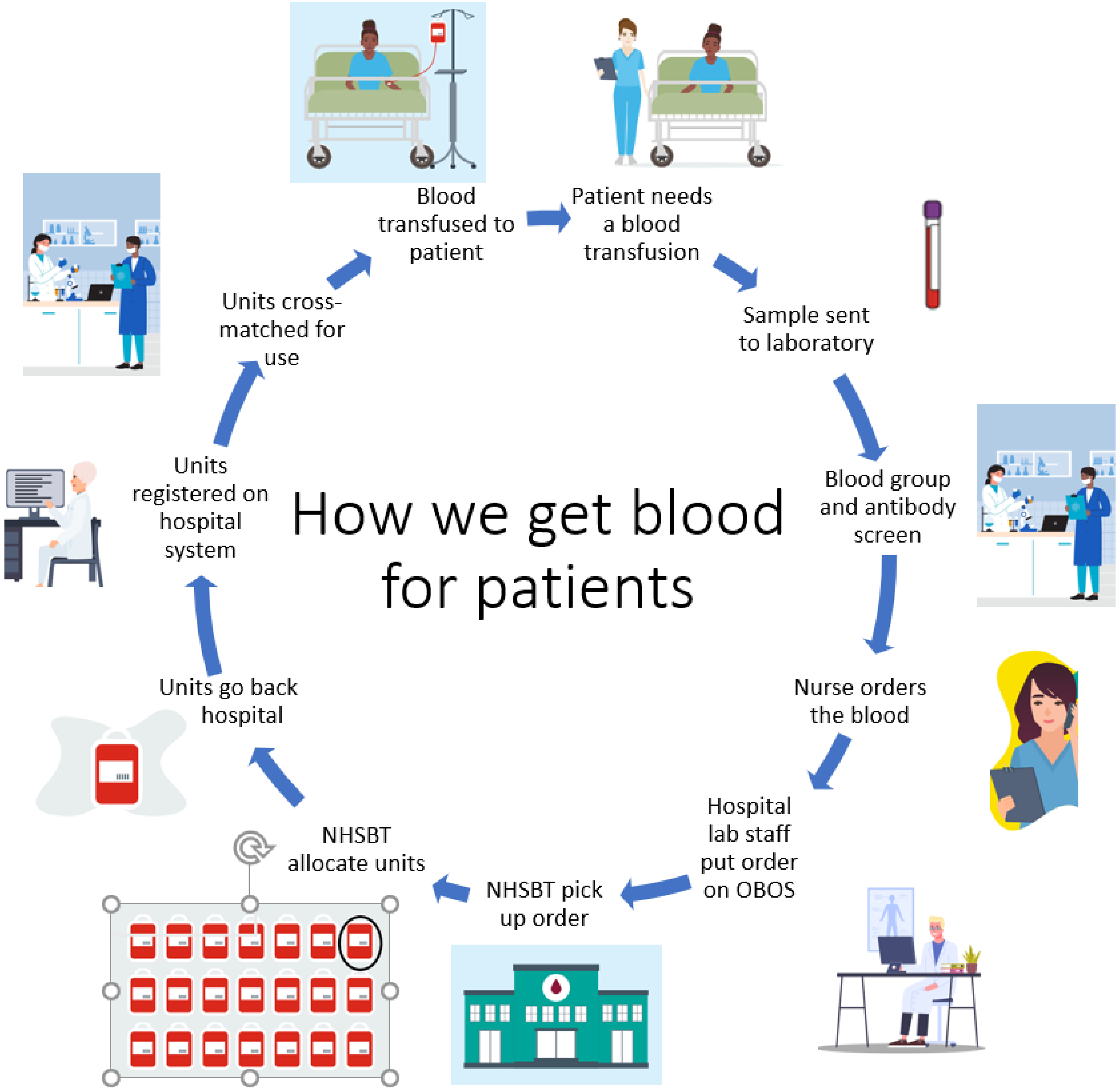
There is a new high throughput, “cheap” genetic test for extended antigen typing

What is the reality of blood matching?

- **Extended typing of donors and patients**
  - Most black donors phenotyped – but we think Rh variants are problematic
  - Only 30% of white donors phenotyped – patchy AND they are 97% of donors
  - Relying on black donors to meet the need of sickle patients is not realistic
- **Numbers of blood groups potentially to match:**
  - >200 blood groups
- **Blood ordering:**
  - done on a group not patient basis



- **Number of units to be matched:**
  - 10,000 units per month for people with sickle in England
- **Available interconnectivity:**
  - There is no meaningful connectivity between NHSBT and hospitals and often within hospitals
- **Selection of blood for transfusion at NHSBT:**
  - Performed manually
- **Stock maintenance and donations:**
  - Not precision managed to meet patient demand
  - A push rather than pull model



So we need three things:

- **Well typed patients** -> Sickle cell and thalassaemia blood group genotyping programme
- **Extended and appropriately typed donors** -> currently under discussion at NHSBT
- **An algorithm to match blood, embedded within NHSBT** -> Haem-Match

Haem-Match?

- To deliver **AI driven genomically matched blood to the patient beside** in order to:
  - **Reduce the risk of harm** caused by transfusion (antibody formation/alloimmunisation/transfusion reactions)
  - **To streamline the allocation of precisely genetically matched units** to patients with complicated transfusion needs
  - **Reduce waste and improve efficiency** in the collection and allocation of blood units.
- Patient cohorts
  - Sickle cell disorder (SCD)
  - Scope this work for other transfusion dependent anaemias such as Thalassaemia and Myelodysplastic Syndrome (MDS).

Haem Match

Haem-Match Funding

BGC

Blood Genomics Consortium

The Blood transfusion Genomics Consortium (BGC) is an international partnership between blood services, research institutions and industry leaders. Their aim is to improve the safety and efficiency of blood and platelet transfusion by introducing cutting-edge genomics technology into routine clinical practice. As the part of the BGC, the national blood services of Australia, Canada, England, Finland, New Zealand the Netherlands, and South Africa together with the New York Blood Center work in partnership with UCLH academic hospitals in Boston and Cambridge, and Thermo Fisher Scientific to develop the DNA-based assays, software solutions, and infrastructure required to implement donor and patient genotyping at global scale. The work of the BGC has been crucial in developing the platform for the genetic blood grouping.

Website

NIHR | University College London Hospitals Biomedical Research Centre

The UCLH Biomedical Research Centre (BRC)

The UCLH Biomedical Research Centre (BRC) is a partnership between University College London Hospitals NHS Foundation Trust (UCLH) and UCL (University College London). The UCLH BRC was established in 2007 as one of five centres that were competitively awarded funding by the National Institute for Health Research (NIHR) to support world leading clinical translational research. In September 2016, the UCLH BRC was awarded £111M for 2017-2022 to enable continued growth in our experimental medicine and early translational research programmes. NIHR UCLH BRC will be funding staff and delivering much of the infrastructure to enable the large scale data collection and analysis needed to support the Haem-Match programme.

Website

NHS Blood and Transplant

NHSBT Research and Development

NHSBT through its Research and Development arm and the organization more widely has been providing some of the initial funds, support and expertise to develop the initial phases of the programme. In addition many of the team are salaried NHSBT employees and part of their work is to support the Haem-Match Programme.

Website

NIHR | National Institute for Health Research

NIHR Artificial Intelligence in Health and Care

The Haem-Match consortium was successful in acquiring funding through a competitive application to the NIHR - AI systems for precision blood group matching. This will fund the salaries of staff that can develop the artificial intelligence programmes that will be needed for the precision blood matching, blood stock maintenance and donor recruitment.

Website

NIHR | Blood and Transplant Research Unit in Donor Health and Genomics at University of Cambridge

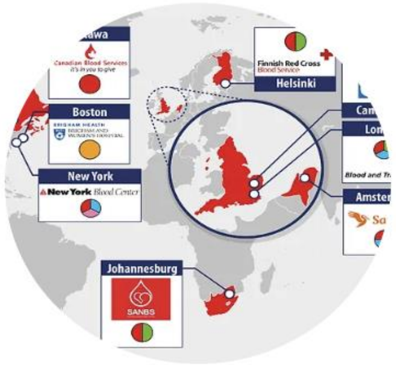
The National Institute for Health Research (NIHR) Blood and Transplant Research Unit (BTRU) in Donor Health and Genomics at the University of Cambridge is a cross-disciplinary unit established to address major questions about the health of blood donors and produce evidence-based strategies to enhance donor safety and ensure sustainability of blood supply. The Unit is funded by the NIHR and is a partnership between the University of Cambridge and NHS Blood and Transplant (NHSBT), in collaboration with the University of Oxford and the Wellcome Sanger Institute. The Public Patient Involvement and Engagement (PPIE) group and the NIHR AI grant work are led through this BTRU.

Website

Sanquin

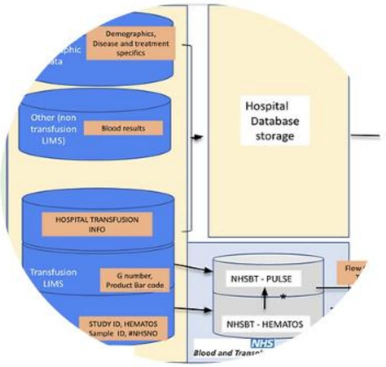
Sanquin is responsible for safe and efficient blood supply in the Netherlands on a not-for-profit basis. Sanquin also develops and produces pharmaceutical products, conducts high-quality scientific research, and develops and performs a multitude of diagnostic services. Researchers at Sanquin including Professor Ellen van de Schoot, Professor Barbera Veldhuisen and Mr Anton van Weert have led the way in the development of antigen typing and the development of AI systems for blood matching and we will be collaborating with them on this and other aspects of Haem-Match.

Website



Blood Antigen Genotyping

WORK PACKAGE 1

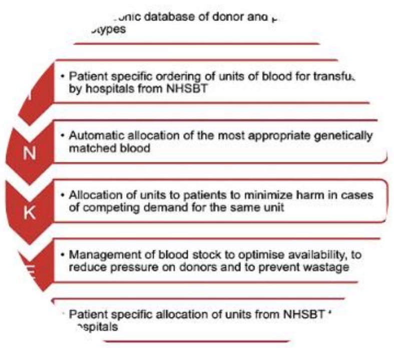


NIHR HIC TDA Database

WORK PACKAGE 2

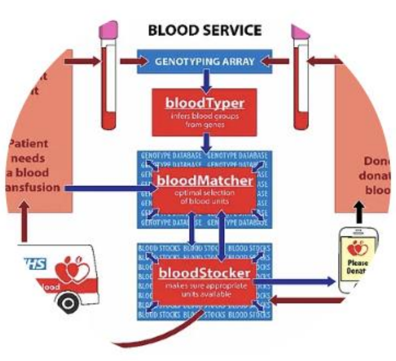
Donor/Patient Demand Modelling

WORK PACKAGE 3



Informatics

WORK PACKAGE 4



Artificial Intelligence

WORK PACKAGE 5

Health Economics

WORK PACKAGE 6

PPIE

WORK PACKAGE 7

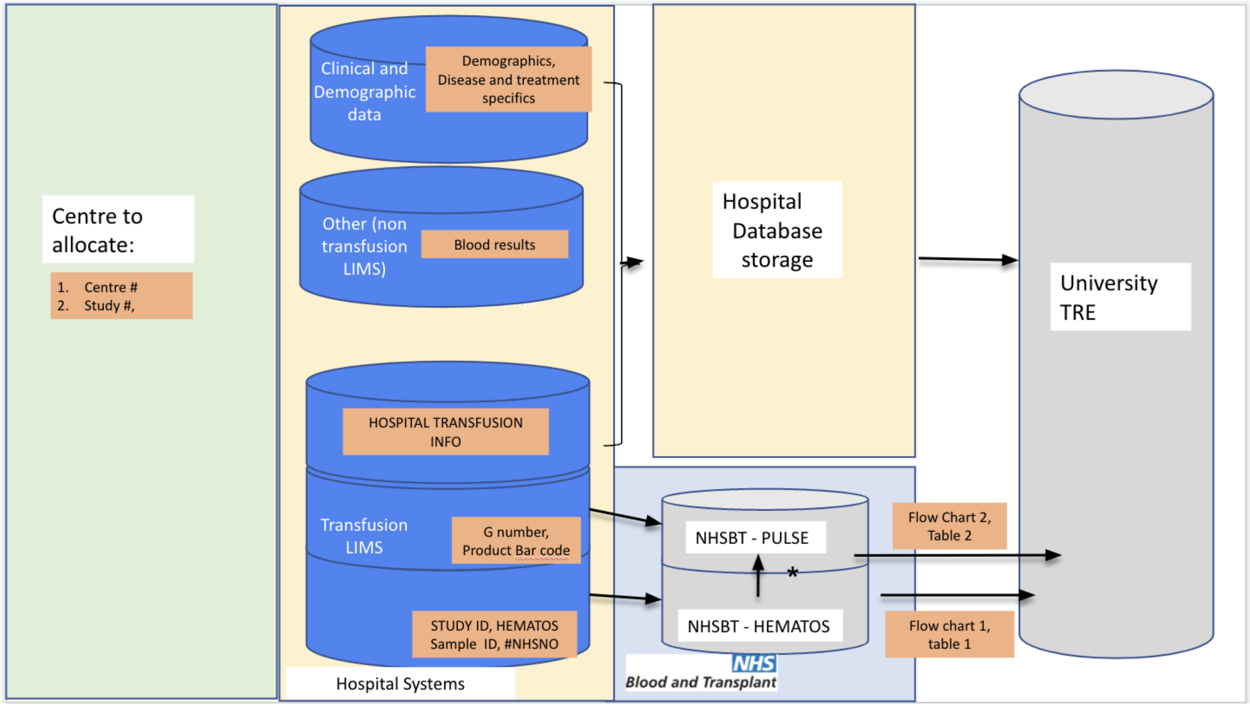
Clinical Studies

WORK PACKAGE 8

Haem Match

Work-Package 2 – NIHR HIC Transfusion Dependent Anaemias (TDA)

- Building the evidence base on which the algorithm will depend
- New theme within the NIHR Health Informatics Collaborative – Transfusion Dependent Anaemias
- Brings together transfusion and clinical data from hospitals and NHSBT to a TRE
- REC approved

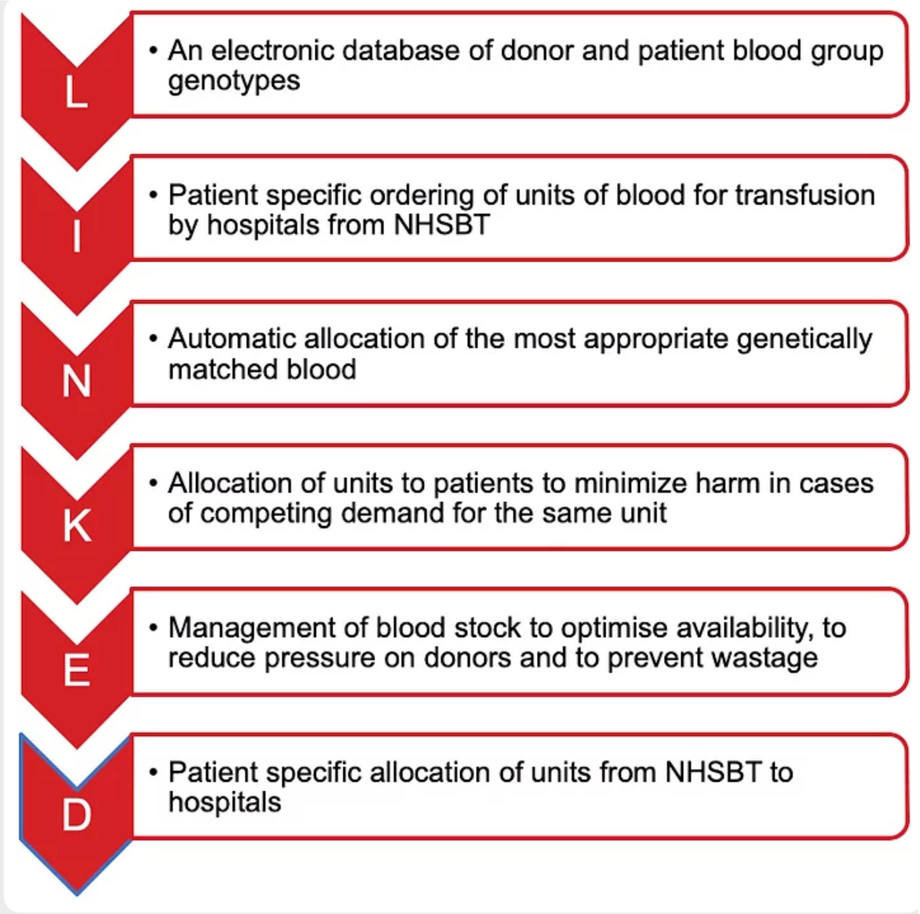


Work Package 3: Donor and Patient modelling

- Multiple sources of information
  - PULSE
  - NIHR HIC
  - HEMATOS
  - INTERVAL/COMPARE/STRIDES
- Approvals through DPIA or ethics as appropriate

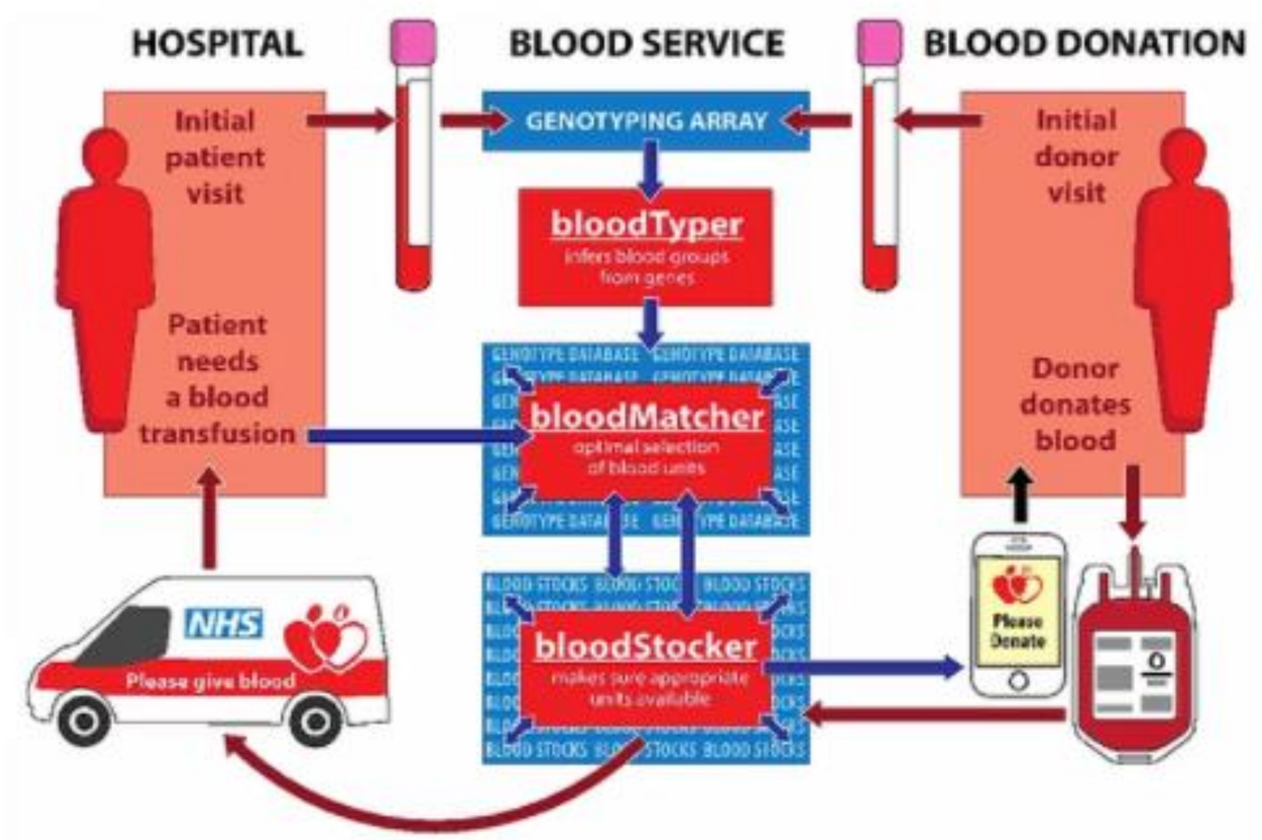
Work Package 4 - Informatics

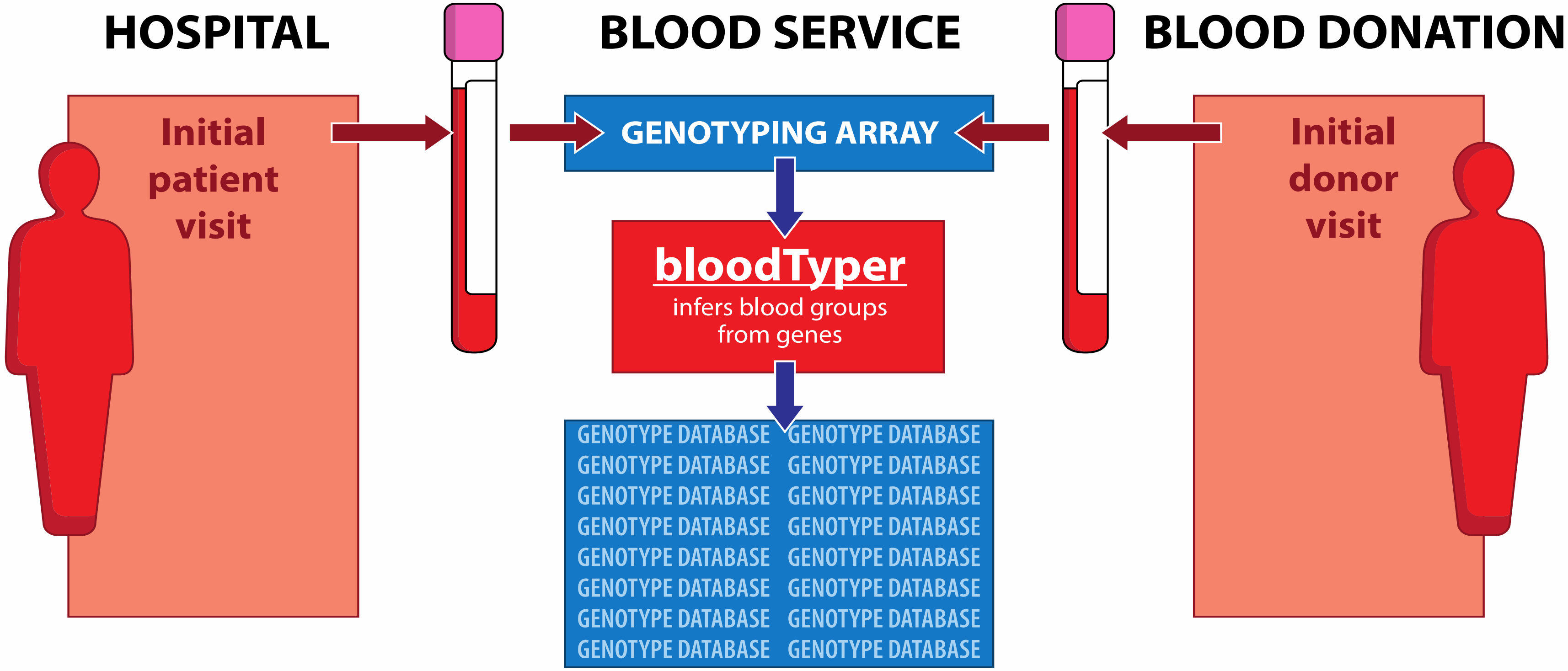
- Part of the Genomics programme for NHSBT
- Searchable database for output of Axiom^{TM} Total Blood Typing Solution designed



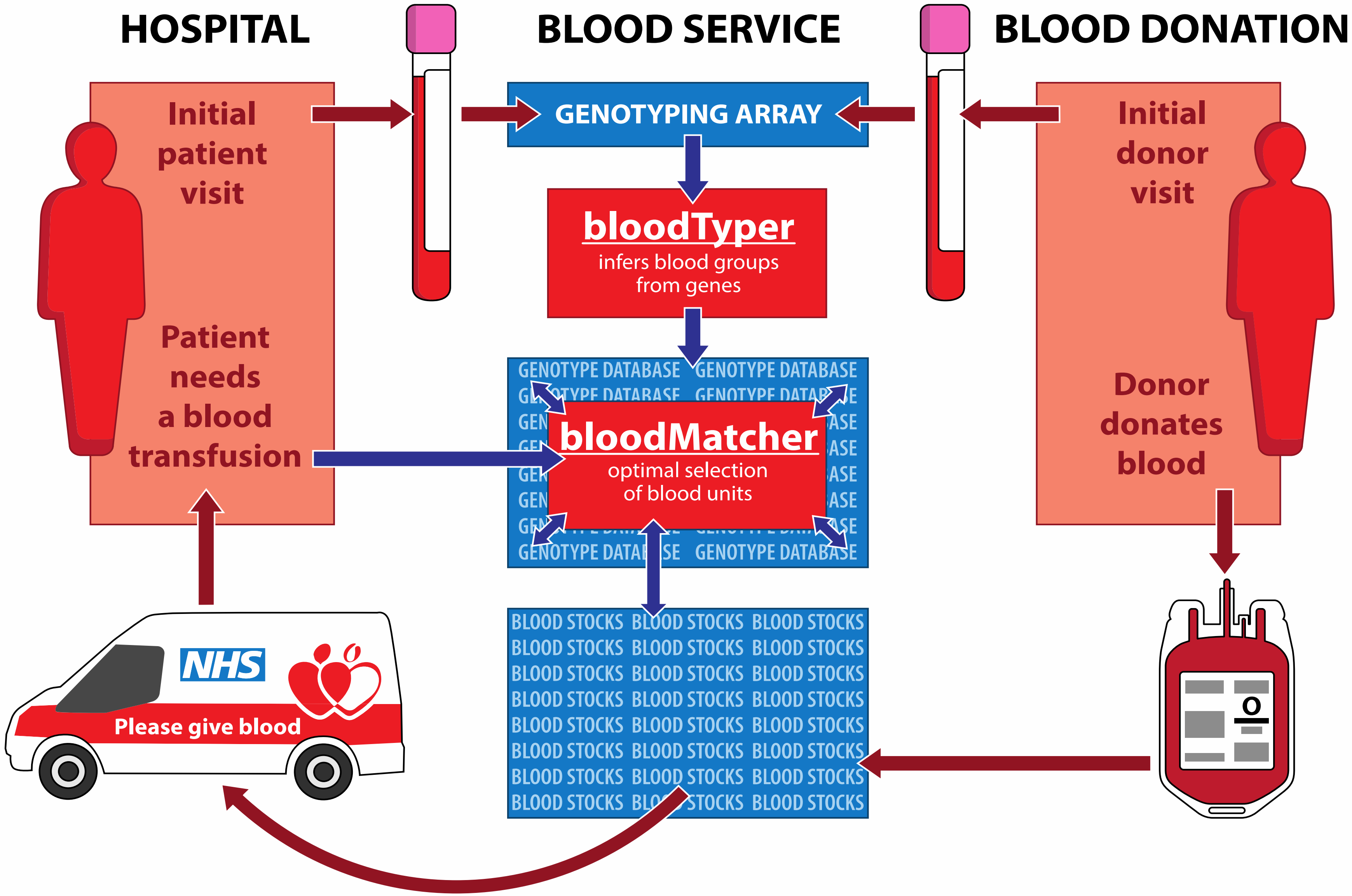
Work Package 5- Matching algorithm

- NIHR AI grant
- £1.23 m

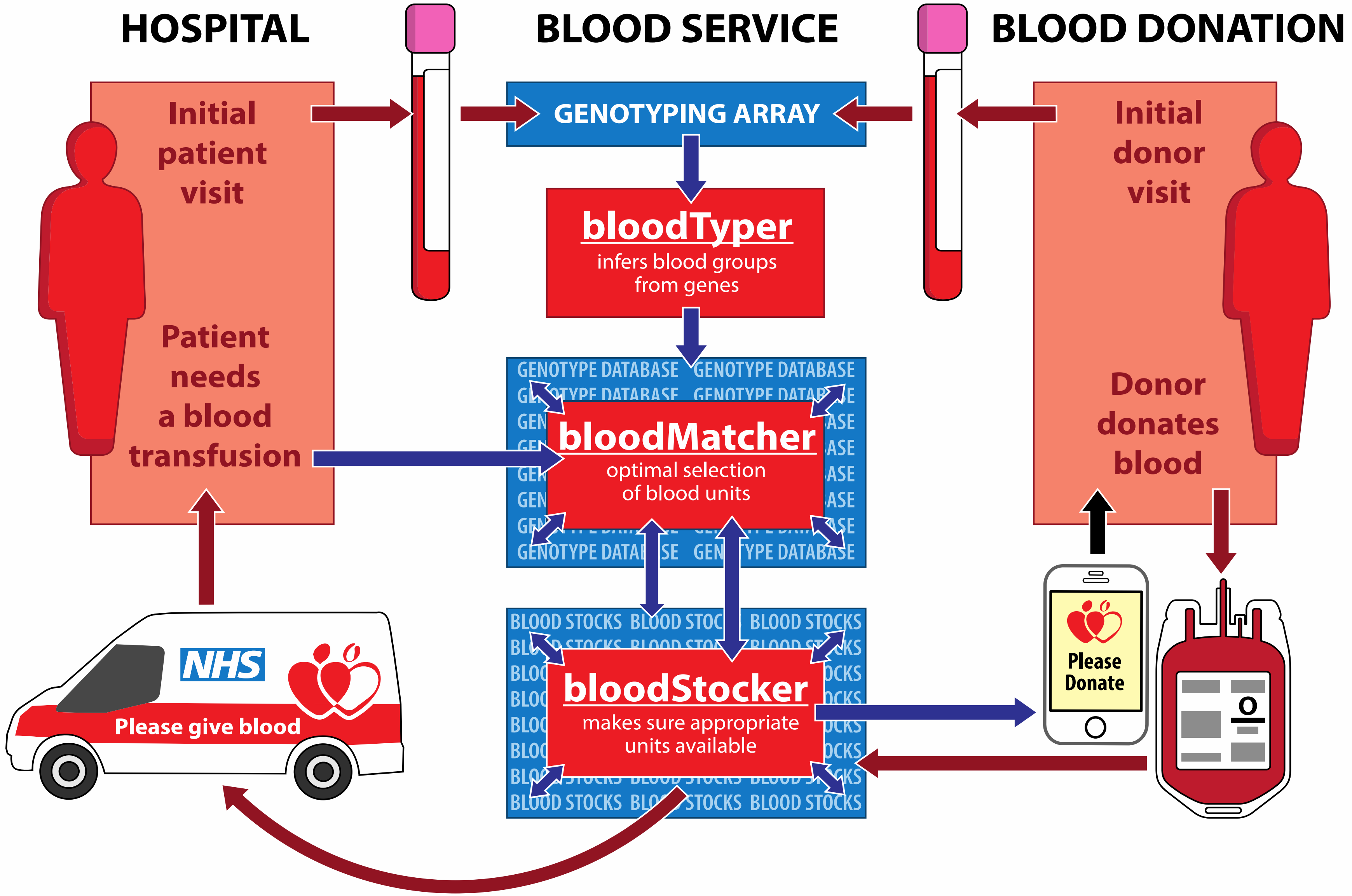




HOSPITAL
BLOOD SERVICE
BLOOD DONATION
Initial patient visit
GENOTYPING ARRAY
Initial donor visit
bloodTyper
infers blood groups from genes
GENOTYPE DATABASE



HOSPITAL
BLOOD SERVICE
BLOOD DONATION
Initial patient visit
Patient needs a blood transfusion
GENOTYPING ARRAY
bloodTyper
infers blood groups from genes
GENOTYPE DATABASE
bloodMatcher
optimal selection of blood units
BLOOD STOCKS
Initial donor visit
Donor donates blood
O
NHS
Please give blood



HOSPITAL
BLOOD SERVICE
BLOOD DONATION
Initial patient visit
Patient needs a blood transfusion
GENOTYPING ARRAY
bloodTyper
infers blood groups from genes
GENOTYPE DATABASE
bloodMatcher
optimal selection of blood units
BLOOD STOCKS
bloodStocker
makes sure appropriate units available
Initial donor visit
Donor donates blood
Please Donate
NHS
Please give blood
O

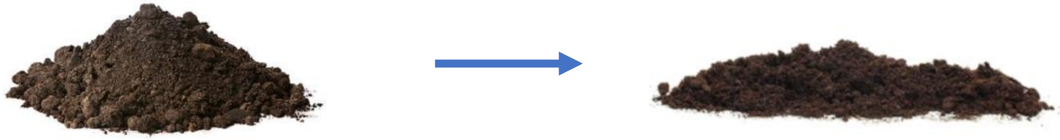
Optimal Transport

Credit for the next few slides:
Dr Nick Gleadall, Dr Folarin Oyebolu, Dr Orod Razeghi

- Problem proposed by Monge in 1781

$$\min_{m, m\#\mu_s=\mu_t} \int c(x, m(x))d\mu_s(x),$$

- What is the most efficient way to move mass between distributions

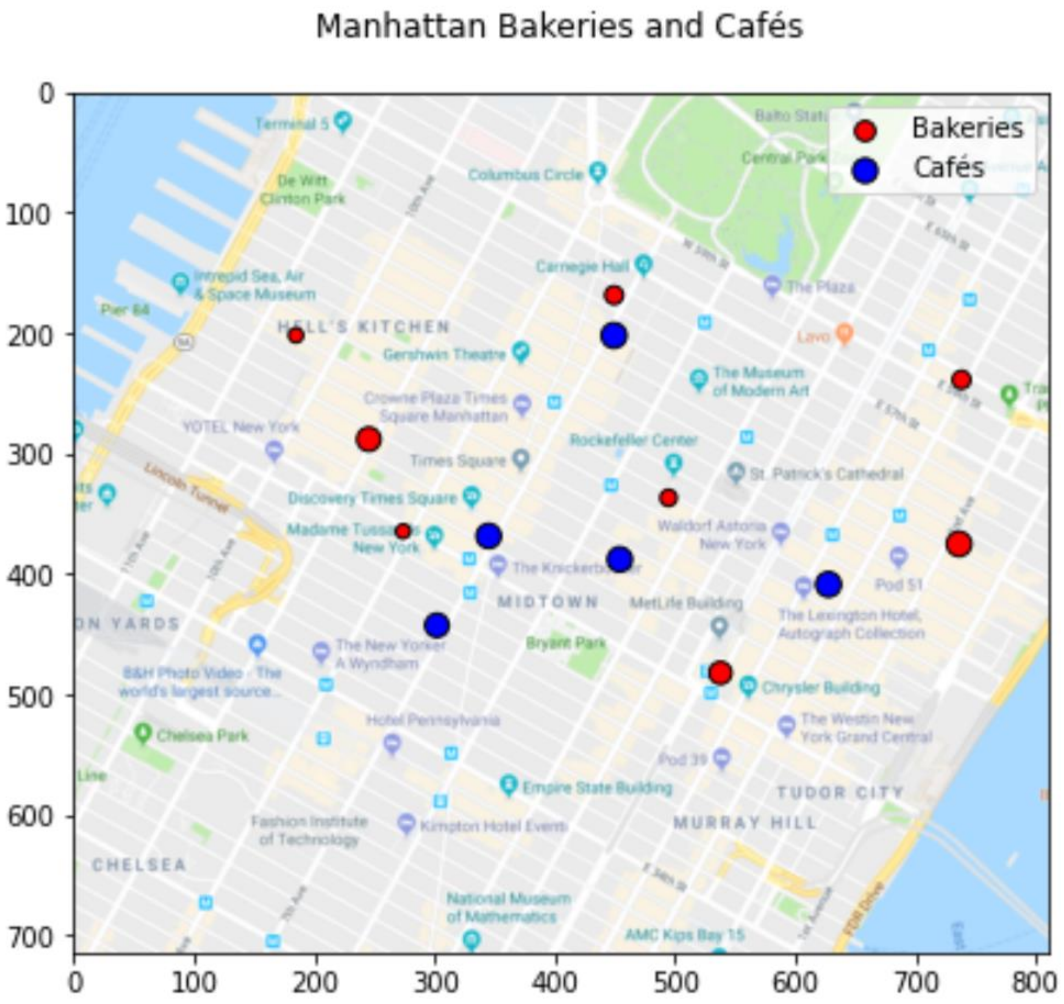


- Linear Program for doing this invented by Leonid Kantorovich in 1940s – **Rare Resource Allocation**

$$\gamma^* = arg \min_{\gamma\in\mathbb{R}_+^{m\times n}} \sum_{i,j} \gamma_{i,j}M_{i,j}$$

$$s.t. \gamma 1 = a; \gamma^T 1 = b; \gamma \geq 0$$

Intuition

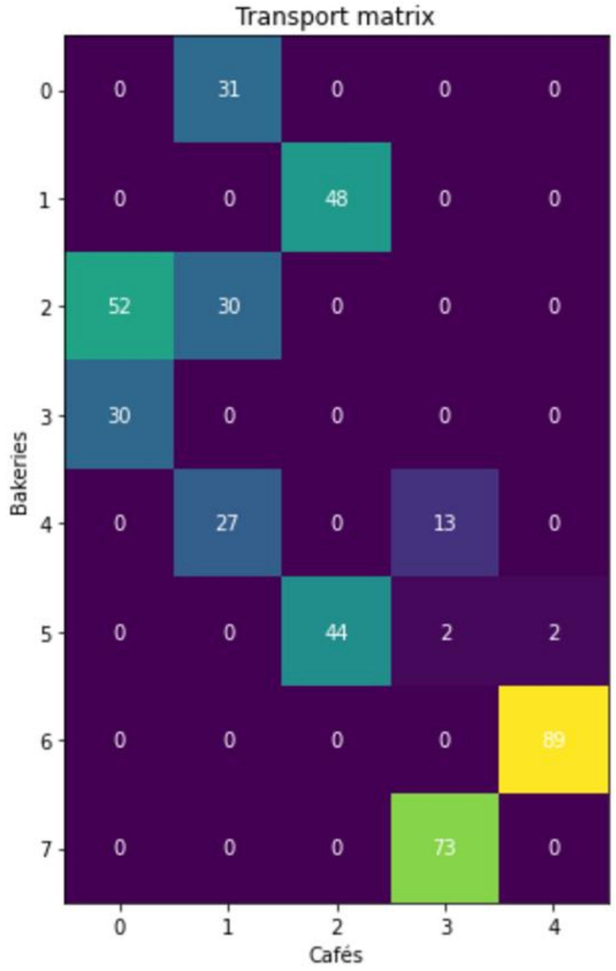


- People love Croissants ( ) for breakfast
- **5 Cafes** in Manhattan sell the best from **8 Bakeries**
- Each **Cafe** sells a different number of :
  82, 88, 92, 88, 91
- Each **Bakery** produces a different number of :
  31, 48, 82, 30, 40, 48, 89, 73

Source: https://pythonot.github.io/auto_examples/plot_Intro_OT.html#sphx-glr-auto-examples-plot-intro-ot-py

Intuition


Manhattan Bakeries and Cafés
0
100
200
300
400
500
600
700
800
HELL'S KITCHEN
MIDTOWN
CHELSEA
TUDOR CITY
MURRAY HILL
Central Park Zoo
Columbus Circle
Carnegie Hall
The Plaza
Gershwin Theatre
The Museum of Modern Art
Rockefeller Center
Times Square
St. Patrick's Cathedral
Waldorf Astoria New York
Bryant Park
Chrysler Building
Empire State Building
Hotel Pennsylvania
Chelsea Park
Intrepid Sea, Air & Space Museum
Pier 84
De Witt Clinton Park
Terminal 5
YOTEL New York
Lincoln Tunnel
Discovery Times Square
Madame Tussauds New York
The New Yorker A Wyndham
B&H Photo Video - The world's largest source...
The Lexington Hotel, Autograph Collection
The Westin New York Grand Central
Pod 51
Pod 39
Fashion Institute of Technology
Kimpton Hotel Eventi
National Museum of Mathematics
AMC Kips Bay 15
Balto Statue
Park Avenue
Lavo
Crowne Plaza Times Square Manhattan
FDR Drive


Transport matrix
Bakeries
Cafés
0 1 2 3 4
0: 0 31 0 0 0
1: 0 0 48 0 0
2: 52 30 0 0 0
3: 30 0 0 0 0
4: 0 27 0 13 0
5: 0 0 44 2 2
6: 0 0 0 0 89
7: 0 0 0 73 0

OT in blood allocation

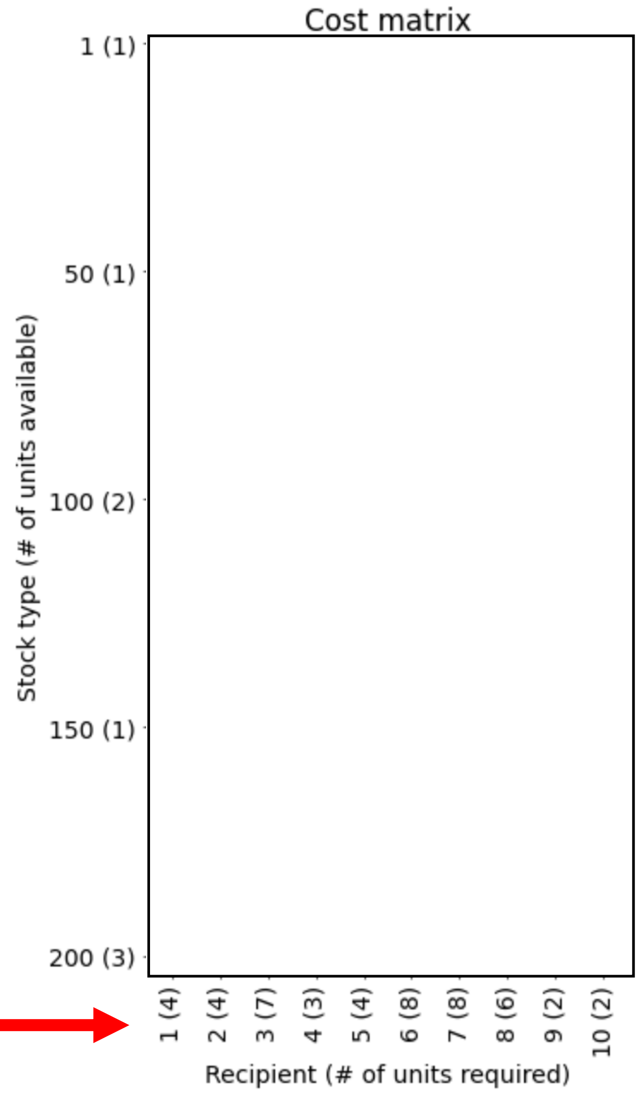
Stock Data (n=2000)

ID	ABO	D	C	E	c	e	K	S	s	Fya	Fyb	Jka	Jkb	Units Available
1	A	+	+	+	+	+	-	-	nan	-	nan	-	+	1
50	A	+	-	+	+	-	-	-	+	-	+	+	-	1
100	B	+	+	-	-	+	-	-	+	-	+	+	+	2
150	O	+	+	-	-	+	-	+	-	-	+	+	-	1
200	O	-	-	-	+	+	-	-	+	-	+	+	-	3

(truncated)

Recipient Data (n=10)

Recipient	ABO	D	C	E	c	e	K	S	s	Fya	Fyb	Jka	Jkb	#
1	B	+	-	-	+	+	-	-	+	+	-	-	+	4
2	A	+	+	+	+	+	+	+	-	+	+	+	-	4
3	A	-	-	-	+	+	-	-	+	+	-	+	+	7
4	O	+	+	-	-	+	-	-	+	+	+	-	+	3
5	A	+	+	-	+	+	-	+	+	+	+	+	-	4
6	O	+	-	+	+	-	-	-	+	+	+	+	+	8
7	AB	+	+	-	-	+	-	-	+	+	-	+	+	8
8	A	+	-	-	+	+	-	+	+	-	+	+	-	6
9	B	-	-	-	+	+	-	-	+	-	+	+	+	2
10	B	+	+	-	-	+	-	+	+	-	+	+	+	2



OT in blood allocation

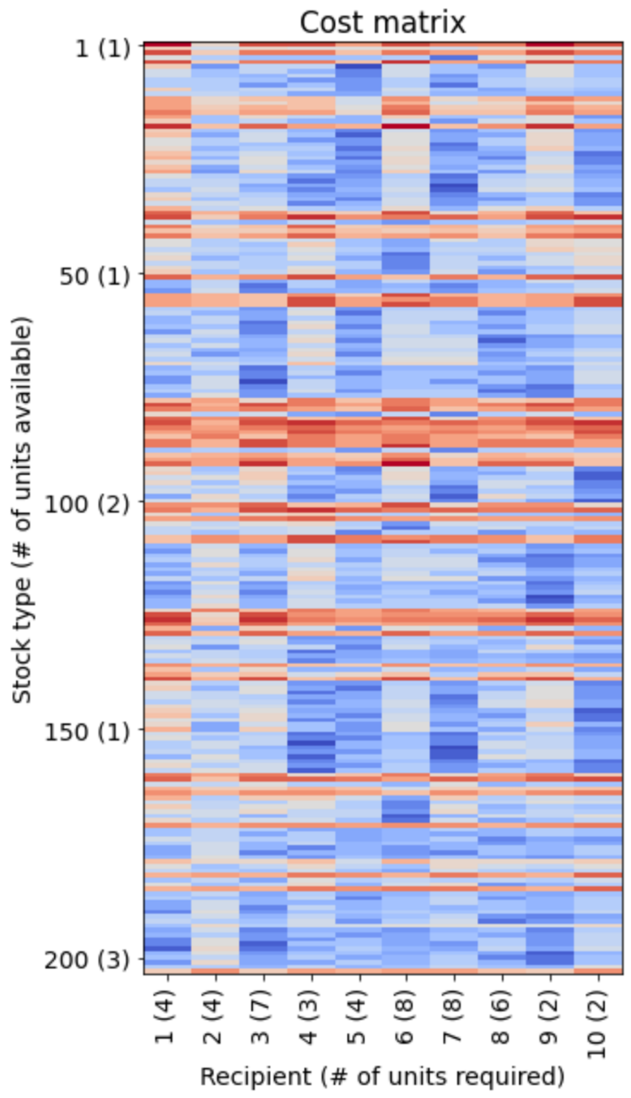
There is an abstract distance between the blood of two people
- Compatibility Distance

In this example, a simple algorithm is applied to all pairwise combinations:

Incompatible (e.g. A -> B or + > -) = Inf

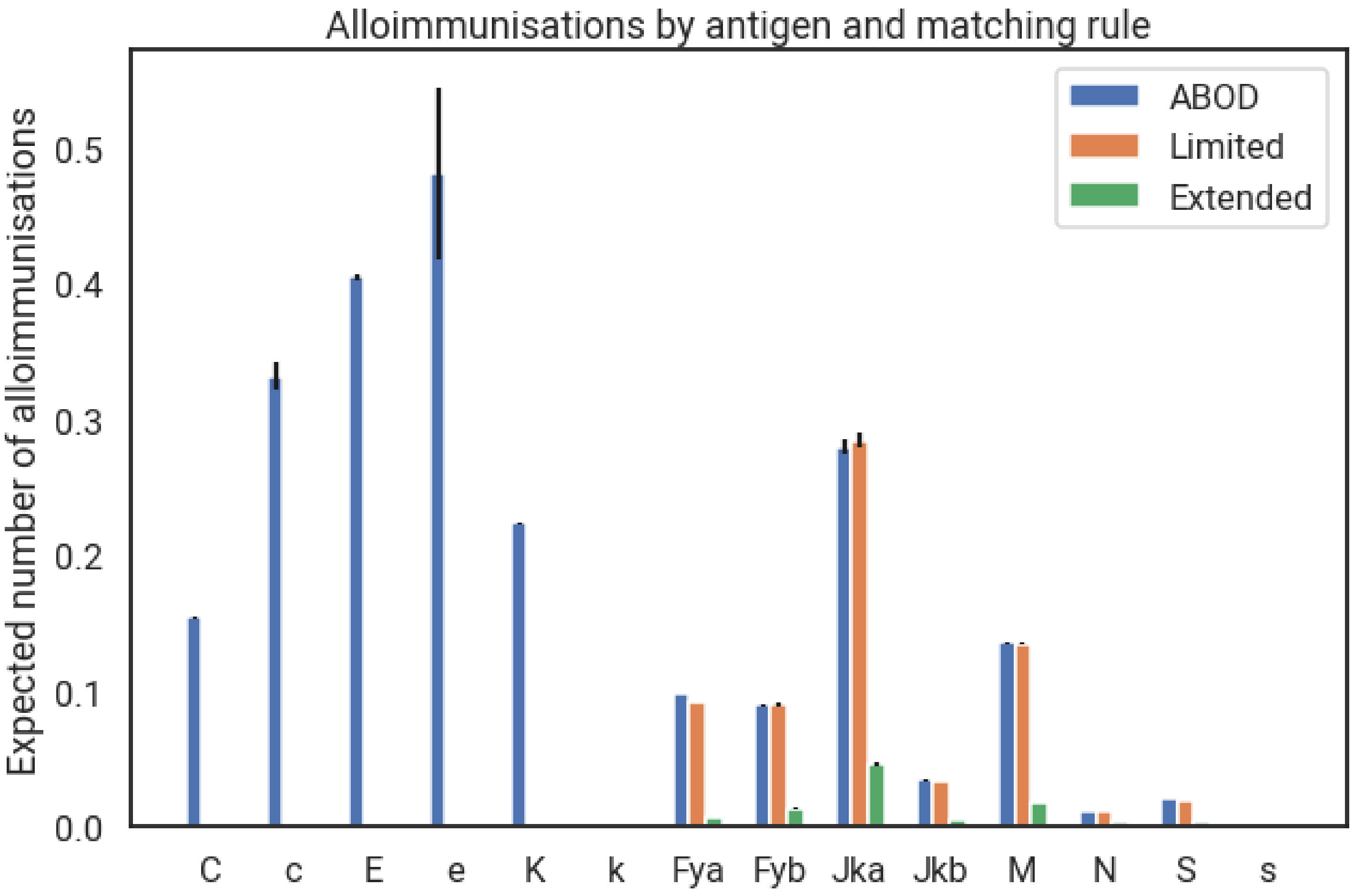
Compatible (e.g. O -> A or - > +) = 0.5

Match (e.g. A -> A , - > - , + > +) = 0



Early Simulations

- Used textbook antigen frequencies to simulate stock & Sickle Cell patient cohort data from UCLH to simulate demand
- Did series of 'on the day' and 6-week time horizon models
- Matching approach works well and significantly reduces expected immunisations over current 'reactive' matching policy



Simulation of matching for six weeks

1386 patients, 10 units each – ~14,000 units in total

	Limited	Extended
Expected number of alloimmunisations	7.92 ± 0.004	**4.10 ± 0.007**
Reduction from Limited	-	**48%**
Expected units short	**3.73 ± 0.145**	**3.74 ± 0.152**

Work Package 6: Health Economics

- NiHR AI Grant plus support from NHSBT
- Based at UCL
- Plotting the whole pathway of blood transfusion -> and comparing our current processes with proposed pathway
- Full health economic evaluation

Work Package 7: Patient Public Involvement and Engagement

- **Patient transfusion panel** established to advise on the project

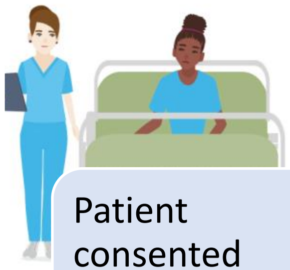
Dr Rachel Kesse-Adu
panel chair

- **Staff transfusion panel** established, including **NHS laboratory staff**

Work Package 8: Feasibility/Pilot study

- Aims:
  - 1°:
    - To evaluate the ability of the Decision Support Algorithm (bloodMatcher) to allocate blood for SCD patients in a single SHU and single hospital
  - 2°:
    - To measure the impact of bloodMatcher on current hospital/NHSBT processes and blood stocks
    - To measure the degree of matching achieved vs standard process

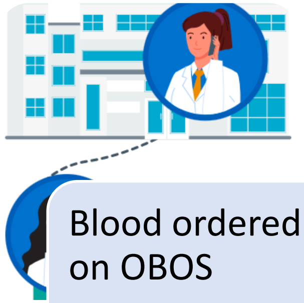
Process: based on HLA matched plts



Patient consented

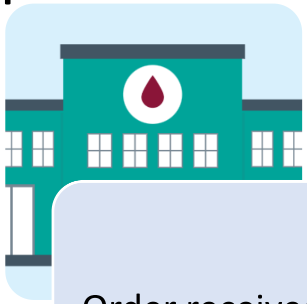
- Has genotype
- Regular exchanges
- Adult

Transfusion scheduled



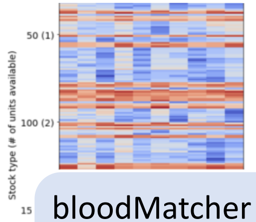
Blood ordered on OBOS

- 8-10 units
- Patient information supplied



Order received at NHSBT

Order intercepted by research team



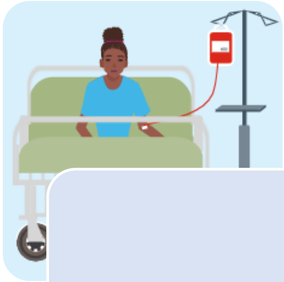
bloodMatcher suggests units

- patient and donor genotyping (HEMATOS)
- donation information (PULSE)

HSST/Consultant double checks allocation

Units formally allocated

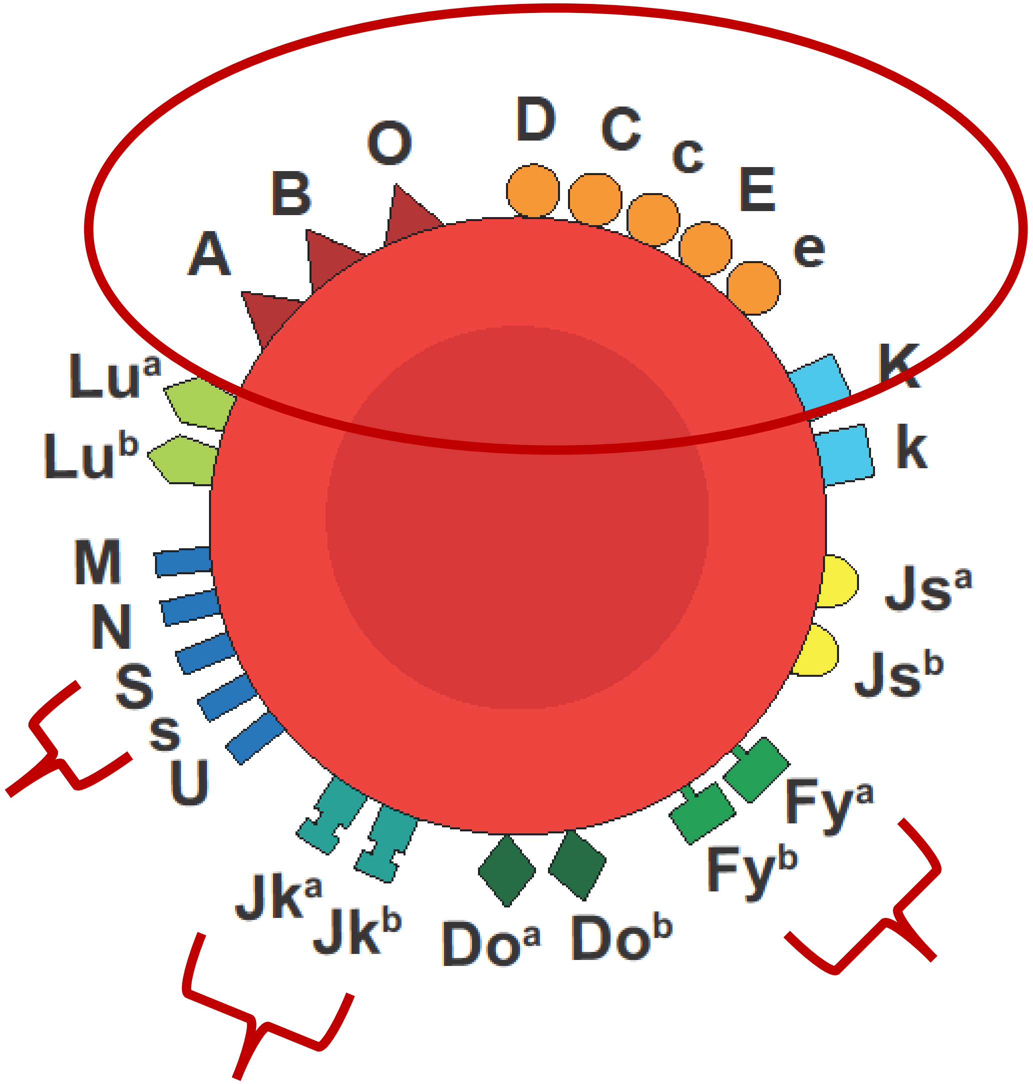
Units issued to hospital



Units transfused

What antigens will we aim to match?

- Based on published evidence
- Algorithm will have to match as per current guidance
- In addition, if stock available and antigen negative, match for Fya, Fyb, S, Jka, Jkb



Feasibility study design

- NHSBT Colindale SHU -> One hospital (UCLH)
- 8 months
- Consented SCD patients, regular planned exchange transfusions
- Pilot – 2-3 patients, November 2024
- De-glitching, December 2024
- Rest of participants mid-January 2025 – mid-June
- Overall: 40 participants, max of 3 exchange transfusions each
- Approximately 40 x 3 x 10 = 1200 units of blood

What next?

- Donor extended typing needs to ramp up
- Feasibility study completed and then funds for a larger multicentre study
- Work on other aspects of automation e.g. bloodstocker

Haem
Match

UNIVERSITY OF CAMBRIDGE

NHS Blood and Transplant

NHS University College London Hospitals NHS Foundation Trust

NHS Cambridge University Hospitals NHS Foundation Trust

UCL

Sara Trompeter
UCL, UCLH & NHS Blood and Transplant

Haem Match

Find out more:

www.haemmatch.org

www.bgc.io

https://www.nhsbt.nhs.uk/what-we-do/clinical-and-research/blood-group-genotyping/

BGC

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